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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,416	07/03/2001	Catherine Dulac	0575/48557-A/JPW/ADM	1905

7590 09/20/2005

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EXAMINER	
PAK, MICHAEL D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,416	DULAC ET AL.	
	Examiner	Art Unit	
	Michael Pak	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32 and 94-99* is/are pending in the application.

4a) Of the above claim(s) *29-32,94 and 95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *96-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Response to Amendment

1. Amendment filed 5 July 2005 has not been entered. Claims 96-99 have been entered and claims 29-32 and 94-95 has been withdrawn. Claims 1-28, 33-93 haven been canceled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's arguments filed 1 June 2005, have been fully considered but they are not found persuasive.

Specification

4. The amendment filed 3 July 2001 remains objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows.

The reason for the objection was set forth in the previous office action.

The amendment to page 19 by addition of the paragraph is new matter. The specification does not disclose the generic structure with the specific amino acid substitutions.

Applicant is required to cancel the new matter in the reply to this Office Action.

Applicants argue that figure 4A and pages 15, 19 and 37 provide support the proposed amendment. However, the figure does not provide support for a generic nucleic acid encoding the proteins with changes. The figure 4A provides support for the specific species only. The amendment to page 19 of the specification is new matter.

Claim Rejections - 35 USC § 101

5. Claims 96-99 remains rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

The reason for the rejection has been set forth in the previous office action.

Applicants argue that it is not necessary for applicants to show conclusive proof of receptor activity, so long as reasonable expectation exists. However, showing the expression of the receptor in vomeronasal gland is not substantial utility because the specification does not teach binding of pheromones to the receptors. Further empirical experimentation is required to determine whether the proteins bind pheromones and if they are pheromone receptor which pheromones the protein binds. The claimed polypeptides do not substantial utility because the skilled artisan would need to prepare, isolate, and analyze the protein in order to determine its function and use. Therefore, the invention is not in readily available form. The polypeptide lacks substantial utility because further research to identify or reasonably confirm a "real world" context of use is required. Thus, the asserted utility lacks substantial and specific utility because further research to identify or reasonably confirm a "real world" context of use is

required. *Brenner V. Manson 383 U.S. 519, 535-536, 148 USPQ 689, 696 (1966)* stated that "Congress intended that no patents be granted on an chemical compound whose sole "utility" consists of its potential role as an object of use-testing ... a patent is not a hunting license." *Brenner* further states that "It is not a reward for the search, but compensation for its successful conclusion." In *Ex parte Fisher* (Bd. Pat. App.Int. Mar. 16, 2004) ("Board Decision") the substantial evidence standard was held to be appropriate based on *Brenner.*

6. Claims 96-99 also remains rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

7. Claims 96-99 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The reason for the rejection has been set forth in the previous office action.

Claims 96-99 encompass the consecutive amino acid sequence which are separated by multiple fragments with the terms "or" which is confusing because the fragments are not the same size. Applicants argue that the commas are clear with the term "or". However, it is not clear which sequences in the claims are part of the

sequential sequence. It is not clear to the examiner if SEQ ID NO:19, 20, or 21 is being described or some other sequence since the loops or the domain are not defined in the SEQ ID NO:19, 20, or 21 nor in the claim. It is not clear where the amino acids corresponds to the SEQ ID NO:. It is not clear whether it is being substituted or these are the sequences and where the corresponding sequences are located.

8. Claims 96-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection and a written description rejection.

The reason for the rejection has been set forth in the previous office action.

Claims 96-99 encompass a subgenus of pheromone receptor with specific amino acid description or substitution. The specification does not disclose the claimed subgeneric pheromone receptor. The specification discloses the species with specific SEQ ID NO: or generic pheromone receptor but not the subgeneric limitation. Claims 96-99 encompass a genus with a large number of nucleic acid molecules whose sequence cannot be envisioned because the claimed nucleic acids are directed comprising language. The essential feature of the claimed nucleic acid molecule is drawn to the orphan receptor whose function is not known because the ligand is not known. One of skilled in the art cannot envision the nucleic acid molecules or the gene comprising the particular sequence. The claims encompass nucleic acid molecule

encoding variants whose structure is not known or nucleic acid molecules encoding other variant proteins with different function from SEQ ID NO:8 taught in the specification. Claimed nucleic acid encoding protein variants encompass a large genus of proteins which are alleles or variants whose function has yet to be identified from different species of animal because the structure of the newly identified naturally occurring protein is not known. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

Newly amended claim 99 encompass a subgeneric limitation which is not supported by page 37 of the specification. The specification refers to a genus of percent identity to comparing the seven sequence on page 37 but not the subgenus of percent identity to SEQ ID NO:8 sequence alone.

Applicants argue that the facts of that case differ fundamentally from those at hand but does explain how it differs. Written description is required because the claims are drawn to a large genus of receptor whose function is not established suffieciently. The specification does not disclose the ligand which binds the putative pheromone receptor and as such cannot envision the large genus of receptor claimed which functions properly.

9. Claims 96-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The reason for the rejection has been set forth in the previous office action.

The determination of whether undue experimentation is needed is based on examining the factors summarized *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Breadth of the claims. The claims 96-98 encompass an isolated nucleic acid encoding an analog, variant, and fragments of a pheromone receptor, and vectors comprising the nucleic acid thereof, because the specification on page 19, lines 16-27, describe a nucleic acid encoding a pheromone receptor to include molecules encoding for polypeptide analog or molecules coding for fragments or derivatives of antigenic polypeptides which differ from naturally-occurring forms in terms of the identity or location of one or more amino acid residues and which share some or all properties of naturally-occurring forms. Claim 99 is drawn to the specific sequence.

The amount of direction of guidance provided. The specification provides guidance in making an orphan G-protein receptor. However, no positive results have been provided showing the ligand which bind the receptors.

The presence or absence of working examples of the invention. The specification provides working examples of how to make and isolated rat nucleic acid molecules of SEQ ID NO:2 which encode the VN1receptors of SEQ ID NO: 8. However, no positive results have been provided showing the ligand which bind the

receptors. No working example of isolated nucleic acid molecule encoding pheromone receptors from any other species from mammals or vertebrates.

The nature of the invention. The nature of the invention is recombinant cloning of cDNA encoding G-protein coupled receptors in the vomeronasal glands using polymerase chain reaction with oligonucleotides designed from conserved regions of G-protein receptors. Invention also provide tissue specific hybridization with the probes prepared based on the sequence of the cDNA isolated.

The state of the prior art. The state of the prior art at the time of the invention was such that one skilled in the art has isolated nucleic acids encoding putative odorant receptors found in the olfactory epithelium and the odorant receptors belong to a family of G-protein coupled receptors based on structural similarity (Buck et al.(U), page 180, figure 5). The state of the art is silent with respect to an isolated nucleic acid molecules encoding pheromone receptors. The state of the art is such that one skilled in the art have shown that steroids such as 16-androstenes, estrenes, and androstenols are pheromones for humans, but the pheromones are species specific (Berliner(B), columns 1-3). At the time of the invention, receptors which bind steroids belong to the family of steroid receptors, and the estrogen receptor and androgen receptor which belong to the steroid receptor family have no structural or functional relationship with G-protein coupled receptors (Wang et al.(V), page 165, figure 4; Buck et al.(U), page 180, figure 5). Steroid receptors are DNA binding proteins whereas the G-protein coupled receptors are seven transmembrane receptors (Wang et al.(V), page 165, figure 4; Buck et al.(U), page 180, figure 5). The state of the art is silent with respect to a G-protein

coupled receptor which binds 16-androstenes, estrenes, or androstenols. The specification fails to provide guidance or working examples to isolate nucleic acids encoding pheromone receptors which bind androstenes or estrenes. Furthermore, the specification fails to provide any ligands for the pheromone receptors. Even after the filing date of the invention, the state of the art indicate that no ligand is known for the pheromone receptors isolated recombinantly (Ryba et al.(W), page 375, second column, second paragraph). Furthermore, even after the filing date of the invention, the state of the art is such that chemicals that act as pheromones are largely uncharacterized (Ryba et al.(W), page 371, first column, last sentence). The state of the art is such that it is not uncommon to isolate orphan receptors where the ligand for the receptors are unknown thus lacking any type of binding assays with the receptor (Watson et al.(X), pages 223-230).

The quantity of experimentation necessary. The state of the art is silent with respect to the relationship of vomeronasal organ in vertebrates outside the mammalian species. For example, in order to make a cDNA library from vomeronasal organ from other vertebrate species from other classes such as lampreys(agnatha-jawless fish), sharks(chondrichthyes-catilaginous fish), marlins(osteichthyes-bony fish), salamanders(amphibians), eagles(birds), and crocodiles(reptiles), one skilled in the art would have to establish phylogenetic relationship of the vomeronasal organ with these other species structurally and functionally. Such determination would require, finding, analyzing, and determining the organs a homologous in evolutionary relationship by showing some type of structural similarity by dissection or microscopy. Once the

structural relationship has been established for the phylogenetic relationship of the vomeronasal organ, then functional relationship has to be established showing pheromonal response to some pheromone and behavior. It should be noted that pheromones for most of the vertebrate species are not known, thus necessitating an empirical determination of the pheromones for many of these species. Assuming that the isolated nucleic acid encoding the naturally occurring pheromone receptor has been identified, since the claims encompass analogs, variants, and fragments, one would test with the ligand the binding to these pheromone receptors. If we take variants only, and using only the naturally occurring 20 amino acids and assuming we use VN1 which has 315 amino acids, then the number of experimentation is 315 to the 20th power which is $9x10^{49}$ number of experiments to determine whether the variants for VN1 are functional.

The predictability and unpredictability. The state of the art discussed immediately above indicate that one skilled in the art could not practice the claimed invention of making and using isolated nucleic acid encoding a pheromone receptor where the pheromone receptors can be analogs, variants, or fragments.

The specification fails to provide guidance or working examples to isolate nucleic acids encoding pheromone receptors which bind androstenes or estrenes because state of the art indicated such steroids bind receptors belonging to family of steroid receptors and not G-protein coupled receptors. Furthermore, orphan receptors without any known ligands such as the pheromone receptors cannot be tested with variants and fragments because without ligand one of skill in the art cannot determine the function of the pheromone receptor using binding assays. One skilled in the art would have to

empirically test chemical compounds to determine whether the ligand binds the orphan receptors.

In view of the extent and the unpredictability of the experimentation required to practice the invention as claimed, one skilled in the art could not make the invention without undue experimentation.

Applicants argue that experimentally proof of receptor activity for the encoded proteins is not needed so long as a reasonable expectation of such activity exists. However, as discussed previously and above, one skilled in the art would require undue experimentation to empirically determine by assaying for which ligand binds the putative pheromone receptor and then determine after finding the function how to use the receptor.

Priority

10. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. However, the continuing application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the claimed invention.

Applicants argue that claimed invention is fully supported by the specification as originally filed as discussed above. However, the 35 U.S.C. 112 rejections are maintained above and the priority is denied.

Claim Rejections - 35 USC § 102

11. Claims 96-99 are rejected under 35 U.S.C. 102(b) as being anticipated by Dulac et al. (Cell, 1995).

The reason for the rejection has been set forth in the previous office action.

Dulac discloses nucleic acid encoding a pheromone receptor which is 100% identical to the claimed SEQ ID NO:8. Burgess discloses vectors and host cells and method of making recombinant protein using the host cell.

Applicants argue that Dulac et al. cannot be cited as prioir art because the application claims benefit of earlier filed applications. However, as discussed above the claims to priority to earlier filed application is not supported and cannot be used to overcome rejections.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak, whose telephone number is (703) 305-7038. The examiner can normally be reached on Monday through Friday from 8:30 AM to 2:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0879.

The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Michael D. Pak

Michael Pak
Primary Patent Examiner
Art Unit 1646
14 September 2005